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PRELIMINARY EXPERIENCE IN THE TREATMENT
OF HYPERTHYROIDISM WITH POTASSIUM
PERCHLORATE*†

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THE observations by MacKenzie (1) and Astwood (2, 3) and their associates of the striking effects of thiourea and related substances upon the thyroid gland have revolutionized the clinical management of patients with thyrotoxicosis. These drugs exert their favorable effect by preventing the incorporation of iodide into molecular combination with tyrosyl groups within the thyroid gland, but they do not prevent the trapping of iodide from the blood by the parenchymal cells of the gland (4). At the present time propylthiouracil, methylthiouracil and 1-methyl-2-mercaptoimidazole (methimazole) are widely employed in the preparation of thyrotoxic patients for surgery, and to a lesser extent in the chronic control of the overactive thyroid gland (5).

Certain simple anionic substances also possess antithyroid activity. Barker (6) in 1936 observed that in patients who receive intensive thiocyanate therapy for hypertension an enlargement of the thyroid gland may develop, which can be reversibly inhibited by adding iodide to the diet. It has been shown that thiocyanate prevents the trapping of iodide by the gland (7). Attempts at using thiocyanate in the treatment of Graves' disease have not been successful, presumably because its antithyroid activity is easily inhibited by small amounts of iodide.

In an investigation of other anionic substances for antithyroid activity in the rat, Wyngaarden, Wright and Ways (8) found that oral or parenteral administration of nitrate or perchlorate inhibits the uptake of iodide by the gland, and causes a release of trapped iodide from the gland. If either sub-

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stance is given continuously in the diet, intense hyperplasia of the thyroid gland results. When compared with iodide, nitrate and thiocyanate, perchlorate is the most potent in preventing the uptake of a tracer dose of radioactive iodine (9).

Perchlorate prevents accumulation of iodide in the thyroid gland of the patient with Graves' disease (10). When perchlorate is given prior to administration of radioiodine, the isotope fails to appear in appreciable concentration in the gland. When radioactive iodide is allowed to accumulate in the thyroid of the methimazole-treated patient, the labeled iodide can be quantitatively discharged from the gland by administering potassium perchlorate.

The effectiveness of perchlorate in preventing access of iodide to the thyroid suggested a therapeutic trial in patients with Graves' disease. This report is a survey of the results which have been obtained in the first 24 patients.

METHODS

The diagnosis of Graves' disease was suspected in each patient because of the classic symptoms and clinical findings characteristic of that disease. Patients with equivocal signs or symptoms and those with nodular goiter were not accepted for this series. The diagnosis in each case, with one exception, was confirmed by demonstrating at least two of the following: a distinct elevation in basal metabolic rate, a high serum concentration of protein-bound iodine, and an increased 48-hour retention of radioactive iodine. In most cases all three tests were made. The dosage of potassium perchlorate was usually 200 milligrams every eight hours, but it was varied slightly for a few patients. The patients were seen at frequent intervals throughout the course of therapy. During the early weeks of treatment the first 8 patients had weekly determinations of the thyroidal uptake of radioiodine, serum concentration of protein-bound iodine and basal metabolic rate, as well as examination of blood and urine. Later these were made at biweekly intervals. Laboratory examinations were performed less frequently on subsequent patients.

When the euthyroid state was achieved, some of the patients underwent subtotal thyroidectomy, some were given iodide in addition to the perchlorate in preparation for surgery, and some received the perchlorate on a continuing basis.

RESULTS

The patients are classified in Table 1 according to plan of treatment. Fourteen patients were prepared for surgery and underwent a subtotal thyroidectomy. Five of these were given saturated solution of potassium iodide for a few days immediately before surgery in order to obtain the

TABLE 1. DISTRIBUTION OF PATIENTS TREATED WITH POTASSIUM PERCHLORATE

Prepared for thyroidectomy		14
Pre-treated with potassium iodide	5	
No pre-treatment with potassium iodide	8	
Escape from iodide control; subsequent preparation with methimazole	1	
Continuously treated—euthyroid		5
Treatment now discontinued	2	
Became euthyroid but escaped from control during potassium iodide therapy		2
Became euthyroid—lost to follow-up		1
Discontinued—? toxic reactions		2
	<i>Total</i>	<i>24</i>

involuting effect of iodide on the hyperplastic gland. In retrospect, 1 and possibly 2 of these patients had begun to escape from complete control after iodide therapy was started. In one of them, a rise in blood pressure and pulse during the surgical procedure necessitated limitation of the operation to a hemithyroidectomy. The opposite lobe was removed uneventfully at a later date, perchlorate being given in the interval. Another of these patients, whose preparation for surgery was marked by a severe attack of recurrent pyelonephritis and who had an uneventful surgical thyroidectomy, was two months pregnant at the time of operation. She had had one child previously but had been unable to conceive for seven years until she became euthyroid during perchlorate therapy. A sixth patient experienced a severe recrudescence of symptoms and signs of thyrotoxicosis after receiving 10 drops daily of a saturated solution of potassium iodide; his scheduled surgery was therefore cancelled. He had been hypothyroid, with a basal metabolic rate of -16 per cent, immediately before the iodide was begun. He was prepared subsequently with methimazole and had an uneventful thyroidectomy.

Eight patients underwent subtotal thyroidectomy without preoperative potassium iodide. There appeared to be little difference in the vascularity of the glands of those patients who received potassium iodide as compared with those who did not, although 1 patient of the latter group had an exceedingly vascular gland which created a difficult problem in hemostasis. One of these patients had a rise in pulse rate to 150 during the operative procedure after half the gland had been removed. Subtotal thyroidectomy was completed at a later date. Perchlorate was given during the intervening time.

Five patients with Graves' disease received perchlorate on a continuous

POTASSIUM PERCHLORATE

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basis and are now euthyroid. Two of these discontinued the drug without recurrence of the disease. Two other patients became euthyroid while taking perchlorate, but when potassium iodide was given in preparation for surgery each experienced a rapid return of the signs and symptoms of thyrotoxicosis. Both are responding again to perchlorate alone. One patient has been lost to follow-up. In 2 of the 24 patients complications developed which necessitated withdrawal of the drug.

Response of the serum protein-bound iodine: The concentration of protein-bound iodine was measured frequently in the serum of the first 8 patients. As may be seen from Figure 1, the modal time of response was four weeks, but there was wide variation in the response rate. The fall in concentration of the blood hormonal iodine appeared to be more rapid than the clinical response or the fall in basal metabolic rate. Later patients showed a fall in serum protein-bound iodine concentration to normal, but usually only initial and final blood determinations were obtained.

Response of the basal metabolic rate: The approach of the basal metabolic rate toward normal is shown in Figure 2 for 20 of the 24 patients. The

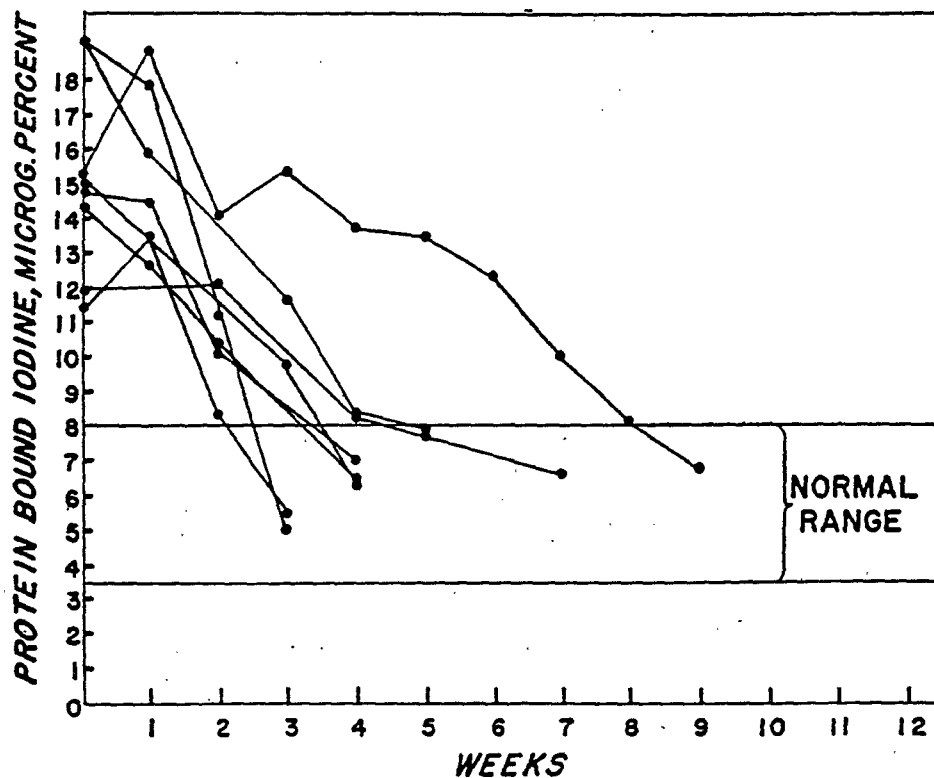


FIGURE 1

modal time required to reach a normal or nearly normal basal metabolic rate was from four to eight weeks, but again there was considerable variation in the response rate. A few patients responded very slowly in spite of an excellent block to accumulation of iodide in the gland.

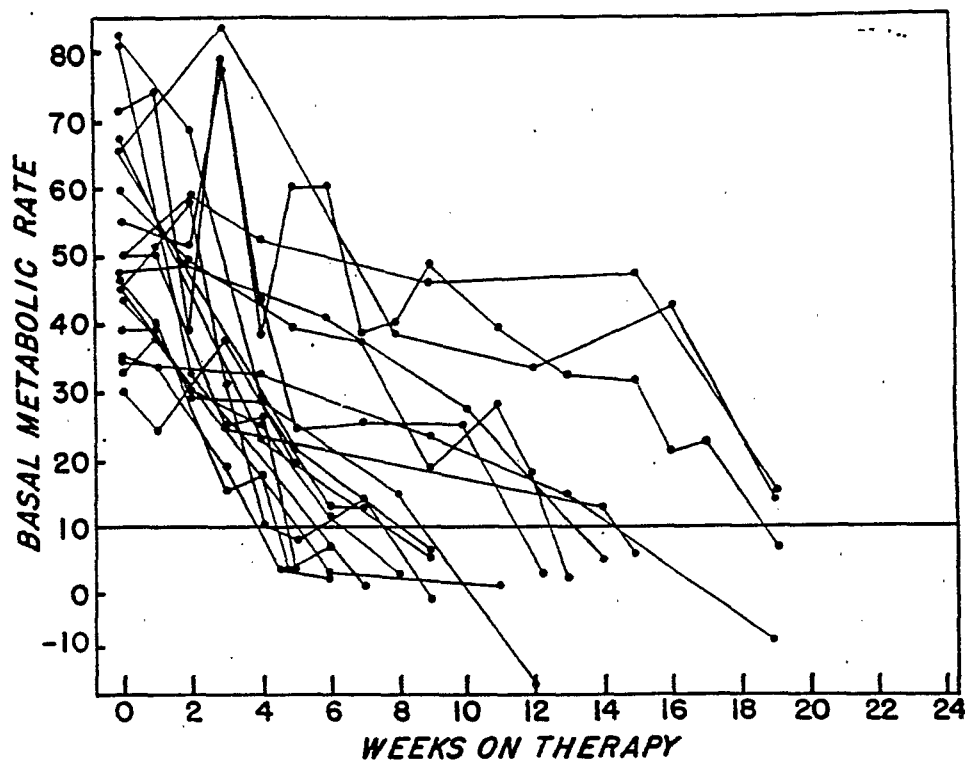
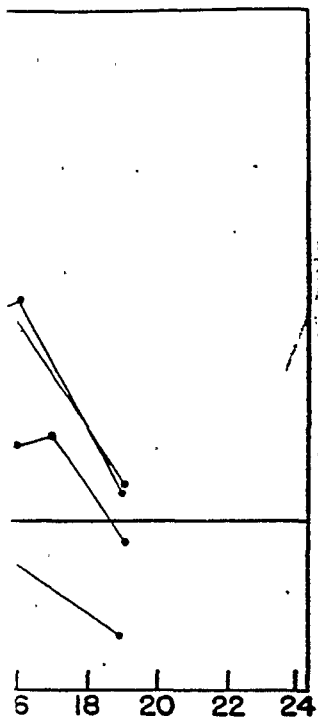


FIGURE 2

Radioactive iodine uptake by the thyroid: This test was performed on all patients before perchlorate was begun. In all but 1 the initial thyroidal uptake determination at forty-eight hours was greater than 60 per cent. One patient who had an uptake of 18 per cent had been taking Lugol's solution until a few days before beginning perchlorate therapy. Her clinical response to perchlorate was slow. Thirteen patients had determinations of the uptake of radioactive iodine both before beginning perchlorate therapy and within two weeks after medication was begun. The mean control uptake was 77.5 per cent, with a range from 60.7 to 108 per cent. The mean uptake during perchlorate therapy was 15.9 per cent, with a range from 3.4 to 38.8 per cent. Only three uptakes were above 20 per cent.

Continuous treatment with perchlorate: Five patients were given perchlorate in order to assess the effects of continuous medication. All 5 became

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euthyroid after a few weeks of treatment and have remained so. The result obtained in these patients is shown in Figure 3. When the drug was discontinued after twenty-eight weeks there was an immediate return of the thyrotoxicosis. Therapy was resumed. The drug was again discontinued after fifty-two weeks but the disease has not returned, although there is still enlargement of the thyroid gland. One patient discontinued medication

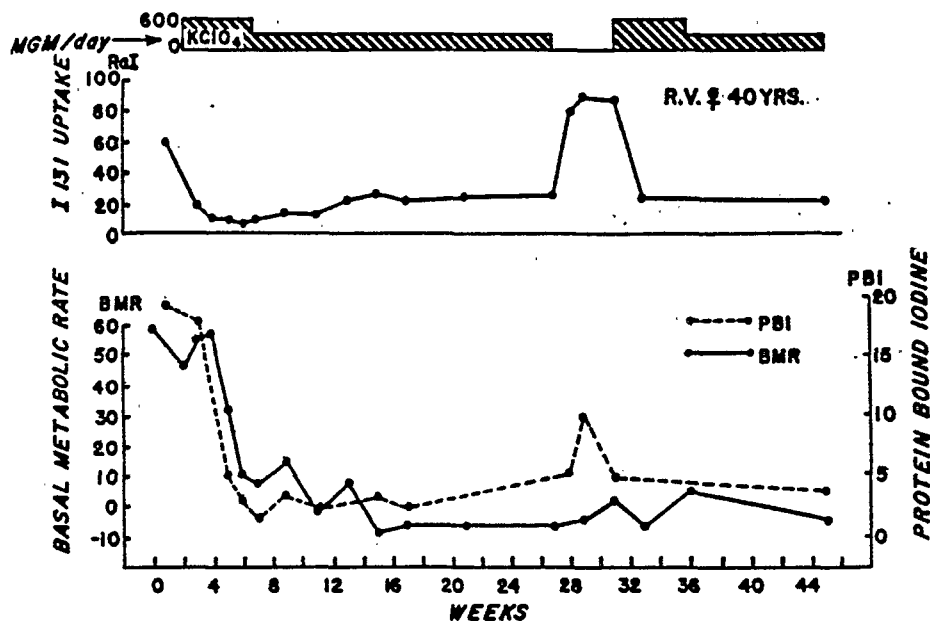


FIGURE 3

after eleven weeks. She failed to keep her appointments and, when seen twelve weeks later, was euthyroid by clinical and by laboratory examination. She has remained so for the intervening five months. It has been possible to reduce the dosage in 2 patients. One is the subject of Figure 3. The other is maintained in the euthyroid state on a single daily dose of 100 milligrams.

Surgical aspects: It was the consensus of the operating surgeons, most of whom were members of the resident staff, that a few of these glands were more vascular than glands of patients prepared in the conventional way with propylthiouracil and iodide. One of the most recent patients to undergo subtotal thyroidectomy seemed to be particularly well prepared by the addition of a single drop of a saturated solution of potassium iodide to the daily perchlorate regimen for a week prior to surgery, but during the same dosage in another patient there was escape from control and a recrudes-

cence of thyrotoxicosis. The problem may be that of achieving the proper balance between the perchlorate and the iodide medication, in order that full advantage may be taken of the blocking effect of perchlorate and the involuting effect of iodide.

There was only one important operative complication. Two patients accumulated fluid in the wound, to a degree sufficient to cause stridor; one required temporary tracheotomy. Two patients had minimal and temporary tetany immediately following operation. One patient had temporary partial paresis of a recurrent laryngeal nerve.

Toxic effects: Perchlorate was withdrawn from 2 patients because of signs and symptoms which might have been toxic manifestations of the drug. One was a 57-year-old woman with mild Graves' disease and congestive heart failure, who had complained of upper gastrointestinal distress and nausea before perchlorate was begun. The symptoms became worse when she was given 200 milligrams of the drug three times daily, but improved when it was withdrawn. She was subsequently treated with radioactive iodine.

The second toxic reaction was more impressive. A 22-year-old secretary with moderately severe Graves' disease of long standing had become severely anorectic a month previous to her first visit to the hospital. A few days after perchlorate was started she began to have burning epigastric discomfort and frequent vomiting. This culminated in a ruptured duodenal ulcer a week later. She was treated without surgery and made an uneventful recovery from the perforation. X-ray examination of the upper gastrointestinal tract disclosed a scarred duodenal cap. She was able to tolerate methimazole without distress, had an uneventful thyroidectomy and is free of symptoms at the present time, but is on a strict medical regimen for her ulcer.

There have been no other toxic manifestations. There were no significant changes in the formed elements of the blood. Two patients were observed to have minimal albuminuria in tests on occasional specimens, whereas there had been no albuminuria before perchlorate was begun. Two patients showed pyuria on occasional tests, while taking perchlorate; one of these had a long history of pyelonephritis. There was no evidence of liver damage, and the only skin rash which was noted disappeared when phenobarbital was withdrawn.

Particular indications: One patient served particularly well to illustrate an especial area of usefulness for potassium perchlorate. A 47-year-old housewife with symptoms of thyrotoxicosis for the previous two years was given methimazole therapeutically four months before entering the hospital. Two weeks later a punctate and urticarial rash and severe arthralgia developed, requiring withdrawal of the drug. She was then given propylthiouracil, but the rash promptly reappeared. Lugol's solution was then

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begun and continued for the next nine weeks. Although she gained a little weight her symptoms of thyrotoxicosis increased. At the time of admission to the hospital her basal metabolic rate was +35 per cent. The signs and symptoms were those of moderately severe Graves' disease. Her therapeutic response to potassium perchlorate was slow, but when she reached the euthyroid state a subtotal thyroidectomy was performed without incident.

DISCUSSION

Potassium perchlorate appears to be an effective agent for controlling the hyperthyroidism of patients with Graves' disease. The symptoms of the disease are mitigated and there is a return to normal of the elevated basal metabolic rate and serum concentration of hormonal iodine. The mode of action of this substance is to deny access of iodide to the thyroid gland.

The rate at which the patient responds to therapy has been found to vary widely, but in general compares favorably with the response rates to antithyroid drugs of the thiourea series (11). No patient has failed to respond in time, but several responded slowly. One of these was receiving large doses of iodine just before perchlorate was begun. Presumably the thyroid of this patient was filled with iodine, which had to be exhausted before a therapeutic effect could be achieved. The other patients who responded slowly had unusually large goiters which were probably filled with stored hormone.

From the surgical point of view the preparation of the gland for excision has left something to be desired. When saturated solution of potassium iodide was given, the thyrotoxicosis of a few of the patients escaped from adequate control. It was long ago shown that a few milligrams of potassium iodide is adequate to involute the thyroid gland of Graves' disease (12). The use of larger doses of perchlorate and smaller doses of iodide may answer the problem of vascularity and escape from control.

The only toxic symptoms which were encountered arose from irritation of the gastrointestinal tract. Although it was by no means certain that perchlorate was responsible for these symptoms or for the duodenal perforation of one of the patients, it must be assumed that this was the case, until further experience has accumulated. Other patients received two to three times the daily dosage of the 2 patients who had gastrointestinal symptoms; yet they did not experience abdominal distress. It remains to be seen whether wider experience with perchlorate will disclose toxic reactions which have not appeared in the present limited series.

SUMMARY

Potassium perchlorate has been used in the treatment of 24 patients with Graves' disease. Oral administration of 200 to 400 milligrams every

eight hours was effective in controlling the disease, as demonstrated by symptomatic improvement of the patient and a return to normal of the basal metabolic rate and serum concentration of protein-bound iodine.

Thirteen patients had subsequent subtotal thyroidectomies. Two patients are euthyroid and have stopped treatment, and the remainder are either being treated continuously or have had their treatment interrupted. Preoperative addition of potassium iodide to the perchlorate caused an escape from control of the thyrotoxicosis in several patients. Two reactions which possibly were toxic manifestations of potassium perchlorate involved the gastrointestinal tract.

Potassium perchlorate is an effective antithyroid agent in the preoperative or continuous treatment of thyrotoxicosis. It is of particular value in those patients who are sensitive to, or fail to respond to the drugs of the thiourea group or iodide. Further experience and study are required for full evaluation of this new antithyroid drug.

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